Cancer Research Consortium of West Michigan
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FAST FACTS

S1400F: (Non-Match sub-study): Anti-PD-1/PD-L1 Resistant – MEDI4736 (Durvalumab) plus Tremelimumab

Eligibility Criteria
Patient must meet the eligibility criteria in Section 5.0 of **S1400F** to be eligible for **S1400F**. If the patient does not meet the eligibility criteria listed in Section 5.1 and Section 5.2 of **S1400F**, submit the **S1400** Notice of Intention Not to Register form and follow patient per Section 7.4 of **S1400**. Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at S1400question@crab.org prior to registration.
In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 7, 14, 16, 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

Sub-Study Specific Disease Related Criteria

1. Patients must have been assigned to **S1400F**.
2. **Patients must have a histologically or cytologically confirmed Stage IV or recurrent pure squamous cell lung cancer.**
3. Patients must have progressed during or after prior platinum-based chemotherapy. For patients whose only prior platinum-based chemotherapy regimen was for Stage I-III disease (i.e. patient has not received any platinum-based chemotherapy for Stage IV or recurrent disease), disease progression on platinum-based chemotherapy must have occurred within one year from the last date that patient received that therapy.
   Patients must also have experienced disease progression during or after anti-PD-1 or anti-PD-L1 antibody monotherapy as their most recent line of treatment. Prior PD-1/PD-L1 combination therapy is not permitted [This criterion replaces common eligibility criteria in Section 5.3b.].
4. Prior exposure to CTLA-4 inhibitors (ipilimumab and tremelimumab) is not permitted. Prior exposure to the following is allowed: attenuated vaccines, anti-EGFR agents, and GM- CSF.
5. Patients must not have received nitrosoureas or mitomycin-c within 42 days prior to sub-study registration.
6. Patients must not have any prior documented autoimmune or inflammatory disease (including inflammatory bowel disease, diverticulitis with the exception of diverticulosis, celiac disease, irritable bowel disease; Wegner syndrome; Hashimoto syndrome) within 3 years prior to sub-study registration. Patients with vitiligo, immune-mediated alopecia, Grave's disease, or psoriasis requiring systemic treatment within the past 2 years are not eligible. Patients with hypothyroidism (e.g. post Hashimoto syndrome) who are stable on hormone replacement therapy are eligible.
7. Patients must not have any history of primary immunodeficiency.

Sub-Study Specific Clinical/Laboratory Criteria

1. Patients must not have received any immunosuppressive medication within 28 days prior to sub-study registration and must not be planning to receive these medications while on protocol therapy. Systemic corticosteroids must be stopped at least 24 hours prior to sub-study registration. However, intranasal and inhaled corticosteroids as well as topical steroids are allowed at any time before and during protocol therapy.
2. Patients must not have experienced a Grade 3 or worse immune-related adverse event (irAE) (except asymptomatic nonbullous/nonexfoliative rash) or any unresolved irAE Grade 2, nor have experienced a toxicity that led to permanent discontinuation of prior anti-PD-1/PD-L1 immunotherapy.

3. Patients must not have any history of organ transplant that requires use of immunosuppressives.
4. Patients must not have any known allergy or reaction to any component of the MEDI4736 (Durvalumab) and/or tremelimumab formulation.
5. Patients must not have clinical signs or symptoms of active tuberculosis infection.
6. Patients must not have received a live attenuated vaccination within 28 days prior to sub-study registration.
7. Patients must not have known HIV, or a known positive test for Hepatitis B virus surface antigen (HBV sAg), or Hepatitis C virus ribonucleic acid (HCV antibody) indicating current acute or chronic infection. Patients with a positive hepatitis C antibody with a negative viral load are allowed. *[This criterion replaces common eligibility criteria in Section 5.3n and 5.3m.]*
8. Patients must have Lipase, Amylase, TSH with reflex Free T3/Free T4 (if TSH is out of normal range) and an EKG obtained within 7 days prior to sub-study registration. Additional timepoints are noted in Section 9.0 Study Calendar.
9. Patients must also be offered participation in banking and in the correlative studies for collection and future use of specimens as described in **S1400F** Section 15.0.

Common Eligibility Criteria for all Sub-Studies

1. Patients whose biomarker profiling results indicate the presence of an EGFR mutation or EML4/ALK fusion are not eligible. Due to existence of approved therapies the biomarker exclusion rules are as follows:

Gene	Alteration type	Ineligible Alteration
EGFR	Substitution	L858R, T790M, A289V, G719A, S768I, G719C, R108K, G598V, R222C, L62R, L861Q, P596L, V774M
	Indel	non-frame shifting insertions or deletions between amino acids 740 and 780, in exons 19 and 20, transcript NM_005228
	Fusion	None
	Amplification	None
ALK	Substitution	None
	Indel	None
	Fusion	EML4-ALK, CLIP4-ALK, CLTC-ALK, KIF5B-ALK, NPM1-ALK, RANB2-ALK, STRN-ALK, TFG-ALK
	Amplification	None

2. Patients must not have received any prior systemic therapy (systemic chemotherapy, immunotherapy or investigational drug) within 21 days prior to sub-study registration. Patients must have recovered (≤ Grade 1) from any side effects of prior therapy. Patients must not have received any radiation therapy within 14 days prior to sub-study registration. (See Section 5.3e for criteria regarding therapy for CNS metastases).
3. Patients must have measurable disease (see **S1400** Section 10.1) documented by CT or MRI. The CT from a combined PET/CT may be used to document only non-measurable disease unless it is of diagnostic quality as defined in S1400 Section 10.1c. Measurable disease must be assessed within 28 days prior to sub-study registration. Pleural effusions, ascites and laboratory parameters are not acceptable as the only evidence of disease. Non-measurable disease must be assessed within 42 days prior to sub-study registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form. Patients whose only measurable disease is within a previous radiation therapy port must demonstrate clearly progressive disease (in the opinion of

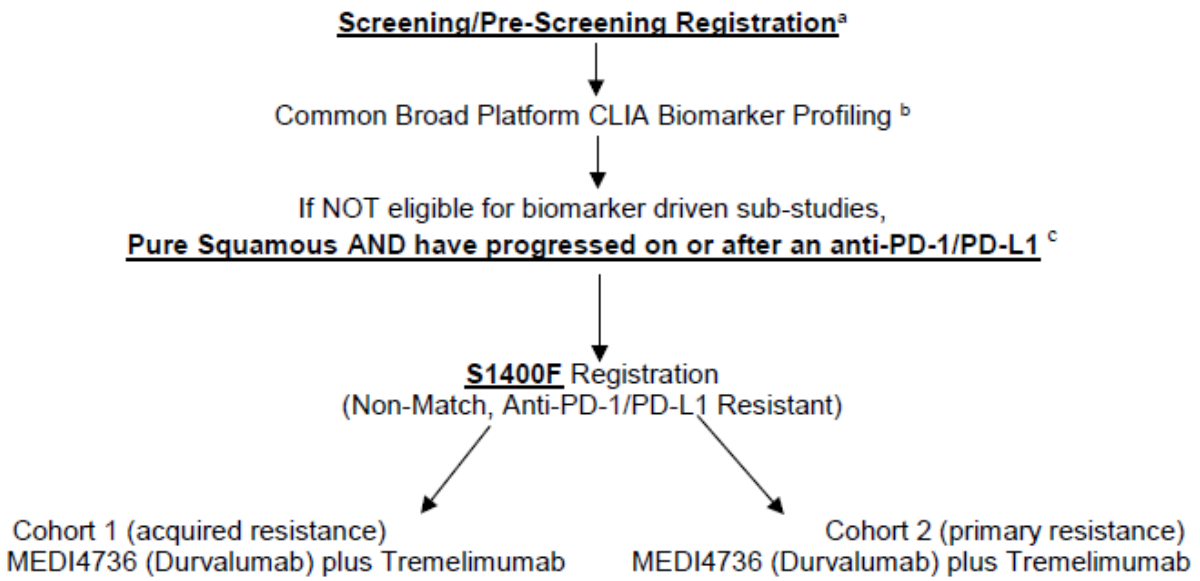
the treating investigator) prior to registration. See S1400F Sections 15.0 and S1400 Section 18.1c for guidelines and submission instructions for required central radiology review.

4. Patients must have a CT or MRI scan of the brain to evaluate for CNS disease within 42 days prior to sub-study registration. Patient must not have leptomeningeal disease, spinal cord compression or brain metastases unless: (1) metastases have been locally treated and have remained clinically controlled and asymptomatic for at least 14 days following treatment, and prior to registration, AND (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least 24 hours prior to sub-study registration.
5. Patient must have fully recovered from the effects of surgery at least 14 days prior to sub-study registration.
6. Patients must not be planning to receive any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.
7. Patients must have an ANC ≥ 1,500/mcl, platelet count ≥ 100,000 mcl, and hemoglobin ≥ 9 g/dL obtained within 28 days prior to sub-study registration.
8. Patients must have adequate hepatic function as defined by serum bilirubin ≤ Institutional Upper Limit of Normal (IULN) and either ALT or AST ≤ 2 x IULN within 28 days prior to sub-study registration (if both ALT and AST are done, both must be < 2 IULN). For patients with liver metastases, bilirubin and either ALT or AST must be ≤ 5 x IULN (if both ALT and AST are done, both must be ≤ 5 x IULN).
9. Patients must have a serum creatinine ≤ the IULN OR measured or calculated creatinine clearance ≥ 50 mL/min using the following Cockroft-Gault Formula. This specimen must have been drawn and proceesed within 28 days prior to sub-study registration:
   Calculated Creatinine Clearance = (140 - age) X (actual body weight in kg†)
   72 x serum creatinine*
   Multiply this number by 0.85 if the patient is a female.
10. Patients must have Zubrod performance status 0-1 (see **S1400** Section 10.4) documented within 28 days prior to sub-study registration.
11. Patients must not have any Grade III/IV cardiac disease as defined by the New York Heart Association Criteria (i.e., patients with cardiac disease resulting in marked limitation of physical activity or resulting in inability to carry on any physical activity without discomfort), unstable angina pectoris, and myocardial infarction within 6 months, or serious uncontrolled cardiac arrhythmia (see **S1400** Section 18.1b).
12. Prestudy history and physical exam must be obtained within 28 days prior to sub-study registration.
13. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for five years.
14. Patients must not be pregnant or nursing. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures
15. As a part of the OPEN registration process (see **S1400** Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current

(within 365 days) date of institutional review board approval for this study has been entered in the system.

16. Patients with impaired decision-making capacity are eligible as long as their neurological or psychological condition does not preclude their safe participation in the study (e.g., tracking pill consumption and reporting adverse events to the investigator).
17. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

SCHEMA



Patients may have screened/pre-screened on **S1400** or **LUNGMAP**
NOTE: At the time of **LUNGMAP** activation, **S1400** screening will close to accrual. Please see Lung-MAP protocol training webpage for additional information (https://www.swog.org/requir lung-map-s1400-training).

Archival formalin-fixed paraffin-embedded (FFPE) tumor, fresh core needle biopsy if needed

Notification of sub-study assignment will be provided by the SWOG Statistics and Data Management Center (see Section 11.0 in S1400 or LUNGMAP for details).